Claims 2-24 are pending. Claims 5, 6, 8, 9, 13, 15, 18 and 21-24 are rejected. Claims 5, 8, 14 and 21 are canceled and claims 6, 9, 13, 15 and 23 are amended. New claims 25-27 are added. The specification has been amended. Applicants have also revised the Sequence Listing by this amendment. Support for the amendments and new claims can be found throughout the application as filed, for example at pages 3-6 and 10 of the specification. No new matter has been added. Applicants request reconsideration and withdrawal of all the rejections.

Disclosure

The disclosure is objected because of the following informalities. The Office Action states that the specification does not contain a brief description of Figures 3-6. The specification at page 5 has been amended to include a brief description of Figures 3-6 as indicated herein.

The Office Action objects to the phrase "subject matter of claims 2 to 10" at page 4 of the specification. The specification has been amended so as to delete the phrase "subject matter of claims 2 to 10" and substitute "subject matter of the further claims" therefore.

Sequence Rules

The Office Action states that the specification fails to recite sequence identifiers at each place a sequence is disclosed, for instance at pages 15 and 21. As indicated herein, the Sequence Listing has been revised and the specification amended to include sequence identifiers where appropriate.

Priority Date

The Office Action states that the application must contain a reference to the earlier priority reference. The specification has been amended to indicate that this application is a divisional application of U.S. Patent Application Serial No. 08/288,508, filed August 10, 1994, now issued as U.S. Patent No. 5,994,094.

Claim Rejections - 35 U.S.C. § 101

The Office Action states that claims 5, 6, 8, 9, 13, 15, 18 and 21-24 are rejected as directed to a product of nature and thus non-statutory subject matter. Applicants note that independent claims 6, 13, and 23 have been amended to recite an "isolated" protein, in accordance with the Examiner's suggestion.

Claim Rejections - 35 U.S.C. § 112, second paragraph

The Office Action states that claims 5, 6, 8 and 9 are as indefinite since they depend from a canceled claim. Claim 5 has been canceled. Claims 6 has been amended to be dependent on claim 13. Claim 8 has been amended so as to be dependent on claim 6 or claim 13.

The Office Action states that claims 8 and 9 are indefinite as a result of the term "usual". Claim 8 has been canceled.

The Office Action states that the phrase "functional parts thereof" of claims 5, 6, 8 and 9 is unclear as what "function" or "parts" are intended. Applicants respectfully disagree. Applicants note that while claim 5 has been canceled, claim 13 has been

amended to include the phrase "functional parts thereof". Applicants point out that the specification at page 5 discloses that the phrase "functional parts" denotes a protein part which is capable of acting as a signal peptide, propeptide or mature part of the protein (*i.e.*, it fulfills a biological function of the natural protein parts of MP-52). The specification also specifically identifies such "functional parts". "Functional part" is defined on page 5, last-but-one-paragraph of the specification, with protein parts being included which must have at least one of the biological functions of the natural protein parts of MP52. No restriction is made to osteogenic or mitogenic activity, but it refers only to the biological functions. For the mature part, of course, this is osteogenic and mitogenic activity, so that all parts of the precursor protein are covered which have said osteogenic and mitogenic functions, regardless of whether they fully correspond to the mature protein part, or whether they are only part thereof. Another possible biological function, however, is also the function as signal peptide and propeptide, respectively, which have the parts upstream of the mature part. Insofar, signal peptide and propeptide, thus, also have biological functions of the natural MP52 precursor protein. The specification at pages 5 to 6 states that the sequence encoding the signal peptide, propeptide and mature part of the protein is nucleotides 640-2142 of SEQ ID NO. 1, with nucleotides 1783-2142 encoding the mature part of the protein. Indeed, such disclosure fully supports new claims 25-27 which have been added in order to more clearly set forth this aspect of the present invention. Applicants urge that no claims are indefinite in light of the phrase "functional parts thereof".

The Office Action states that claims 8, 9, 15, 21 and 22 are indefinite for reciting the term "auxiliary". Applicants respectfully disagree as the phrase "auxiliary

substances" are commonly known to those of skill in the pharmaceutical arts. Applicants note that such "auxiliary substances" are commonly known to include substances such as buffers and solubilizers. Those of skill in the art would understand such "auxiliary substances" to refer to those substances which can be used as part of the intended formulation but which do not represent the active agent. Applicants urge that the claims are definite.

The Office Action states that claims 5, 6, 8, 9, 13, 15, 18 and 21-23 are indefinite for reciting the term "mature". Applicants respectfully disagree. Applicants point to the specification at pages 4 and 5 which indicates that SEQ ID NO. 1 shows the complete nucleotide sequence of the DNA coding for the TGF-β protein MP-52, with the "mature" part of the protein corresponding to nucleotides 1783-2142 of the sequence. Those of skill in the art viewing the specification would clearly find the claims to be definite.

The Office Actions states that claims 13, 15, 18, 21 and 22 are indefinite in light of the phrase "stringent conditions". As indicated herein, independent claim 13 has been amended so as to delete reference to the phrase "stringent conditions". Applicants respectfully submit that the claims are definite.

The Office Action states that claims 21 and 22 are indefinite because it is unclear whether the "matrix" is in addition to or is the carrier, substance, diluent or filler. Applicants note that claim 15 has been amended to recite "further comprising a pharmaceutically acceptable carrier . . .", so as to indicate that the matrix of claims 21 and 22 is in addition to the carrier, auxiliary substance, diluent or filler.

Finally, the Office Action states that claim 23 is indefinite for reciting the phrase "signal and/or propeptide parts". Applicants note that claim 23 has been amended to

recite "signal peptide or propeptide", in accordance with the Examiner's suggestion. Applicants further note that the specification at pages 5 to 6 identifies such signal and propeptide parts, the specification disclosing that the sequence encoding the signal, propeptide and mature part of the protein is nucleotides 640-2142 of SEQ ID NO. 1, with nucleotides 1783-2142 encoding the mature part of the protein.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The Office Action states that claims 5, 6, 8, 9, 13, 15, 18, 21 and 22 are not enabled for polypeptides encoded by polynucleotides that hybridize to SEQ ID NO: 1 and allelic variants of SEQ ID NO: 1. Applicants urge that this rejection is obviated in light of the cancellation of independent claim 5 and the amendment of independent claim 13 so as to delete reference to stringent hybridization conditions.

The Office Action states that claims 8, 9, 15, 18, 21 and 22 are not enabled for the prevention or treatment of all of the tissues or conditions listed in claim 9. Claim 9 has been amended so as to be directed to pharmaceutical compositions suitable for the treatment of bone, cartilage and connective tissues and teeth. Applicants have also added new claim 26 which is directed to pharmaceutical compositions for application in cases where angiogenesis is advantageous or desired. Applicants note that it is well known to those of skill in the art that proteins similar to TGF-β are multifunctional and that such proteins can be used in connection with diseases other than bone applications. Applicants also point out that since MP-52 is a member of a large protein family, assay systems tested for other protein members of the family are readily

available to those of skill in the art. It is therefore much easier to detect efficacy for the proteins of the claimed invention than for a single protein, the environment of which would be unknown.

Finally, the Office Action states that the specification is not enabling for a composition wherein the active ingredient is optional as in claims 8 and 9. Applicants note that claim 8 has been canceled.

Claim Rejections - 35 U.S.C. §§ 102(e) and 103

The Office Action states that claims 5, 6, 8, 9, 13, 15, 18 and 21 are either anticipated by or obvious over Lee et al. (U.S. Patent No. 5,801,014). Applicants respectfully disagree. Applicants note that independent claim 5 has been canceled simply to advance prosecution. Independent claim 13 has been amended as indicated herein. Applicants urge that Lee et al. does not teach or suggest any of the sequences set forth in sections a), b), c), d) or e) of claim 13. The Lee et al. reference simply discloses a mouse sequence and indicates in Example 1 that only partial sequences from a part of the human mature protein show no amino acid deviation. Such disclosure provides no indication of the complete sequences as set forth in a), b), c), d) or e) of claim 13. Applicants therefore urge that Lee et al. does not teach or suggest the claimed invention.

Applicants respectfully urge that in light of the discussion above, the claimed invention is in condition for allowance and request early notification to that effect. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants'

undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,

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IN THE CLAIMS:

Please amend claims 6, 9, 13, 15 and 23 as follows.

Claim 6 (Amended). [Protein] The isolated protein as claimed in [claim 5] claim 13, wherein

[it] the protein has the amino acid sequence shown in SEQ ID NO. 2 or [, if desired,] functional parts thereof.

Claim 9 (Amended). [Pharmaceutical] The pharmaceutical composition as claimed in claim 15 [8], wherein the pharmaceutical composition is suitable for the treatment of bone, cartilage and connective tissues or teeth [for the treatment or prevention of damage to bone, cartilage, connective tissues, skin, mucous membranes, epithelium or teeth, for application in dental implants and for application in wound-healing and tissue regeneration processes].

Claim 13 (Amended). [A protein] An isolated protein of the TGF-β family encoded by an isolated DNA molecule which [has] comprises a sequence selected from the group consisting of:

a) the sequence shown in SEQ ID NO:1,

b) a part of SEQ ID NO:1 which encodes the mature protein,

c) a nucleotide sequence which encodes the amino acid sequence according to SEQ ID NO:2,

d) a nucleotide sequence which encodes a portion of the amino acid sequence according to SEQ ID NO:2, wherein said portion is the mature protein, and

e) the sequence according to a), b), c) or d) which encodes at least a functional part of the protein of the TGF-β family, wherein the functional part maintains essentially the same osteo-inductive and/or mitogenic activity of the mature protein, and

[e) a sequence which hybridizes to a), b), c) or d) under stringent hybridization conditions, wherein said sequence encodes the mature protein of the TGF-β family.]

f) a nucleotide sequence which encodes a portion of the amino acid sequence according to SEQ ID NO:2, wherein said portion is the signal or propeptide part.

Claim 15 (Amended). A pharmaceutical composition comprising at least one protein according to claim 6, [13, in combination with] further comprising a pharmaceutically acceptable carrier, auxiliary substance, diluent or filler.

Claim 23 (Amended). [A protein] An isolated protein of the TGF-β family encoded by a DNA molecule which comprises the [is] part of SEQ ID NO:1 which encodes the mature protein and further comprises nucleotide sequences coding for [signal and/or propeptide] at least one of signal peptide or propeptide parts.

IN THE SPECIFICATION:

Please amend the first full paragraph of page 4 of the specification as follows.

Further embodiments of the present invention concern the subject matter of [claims 2 to 10] the further claims. Other features and advantages of the invention can be derived from the description of the preferred embodiments and figures. The sequence protocols and figures are now briefly described.

Please amend the paragraph spanning pages 13 and 14 of the specification as follows.

The clone was completed up to the 3' end of the cDNA according to the method described in detail by Frohmann (Amplifications, published by Perkin-Elmer Corp., Issue 5 (1990), pp 11-15). The same embryonic mRNA that had been used to isolate the first fragment of MP-52 was reversally transcribed as described above. The amplification was carried out using the adapter primer (AGAATTCGCATGCCATGGTCGACG) (SEQ ID NO:3) of the MP-52 sequence. The amplification products were reamplified using an overlapping adapter primer (ATTCGCATGCCATGGTCGACGAAG) (SEQ ID NO:5) and an overlapping internal primer (GGAGCCCACGAATCATGCAGTCA) (SEQ ID NO:6) of the MP-52 sequence. After restriction cleavage with NcoI the reamplification products were cloned and sequenced into a vector that was cleaved in the same way (pUC 19 (Pharmacia No. 27-4951-01) having a modified multiple cloning site which contains a single NcoI restriction site) and sequenced. The clones were characterized by their sequence overlapping at the 3' end of the known MP-52 sequence. One of these was used as a probe to screen a human genomic gene bank (Stratagene No. 946203) according to a method described in detail by Ausubel et al. (Current Protocols in Molecular Biology, published by Greene Publishing Associates and Wiley-Interscience (1989)). One phage (λ2.7.4) was isolated from $8x10^5$ λ phages which contained an

insertion of about 20 kb and which is deposited at the DSM under the depository number 7387. This clone contains further sequence information at the 5' end in addition to the sequence isolated from mRNA by the described amplification methods.

Please amend the paragraph spanning pages 14 and 15 of the specification as follows.

The genomic DNA contains an intron of about 2 kb between base paris 1270 and 1271 of SEQ ID NO:1. The sequence of the intron is not shown. The correctness of the splicing site was confirmed by sequencing an amplification product which was derived from cDNA containing this region. These sequence informations were obtained using a slightly modified method which is described in detail by Frohmann (Amplifications, published by Perkin-Elmer Corporation, Issue 5 (1990), pp 11-15). The same embryonic RNA that was also used to isolate the 3' end of MP-52 was reverse transcribed using an internal primer orientated in the 5' direction of the MP-52 sequence (ACAGCAGGTGGGTGGTGTGGACT) (SEQ ID NO:7). A polyA tail was attached to the 5' end of the first cDNA strand using terminal transferase. A two-step amplification was carried out, firstly by using a primer composed of oligo dT and an adapter sequence (AGAATTCGCATGCCATGGTCGACGAAGC(T16)) (SEQ ID NO:8) and secondly an adapter primer (AGAATTCGCATGCCATGGTCGACG) (SEQ ID NO:3) and an internal primer (CCAGCAGCCCATCCTTCTCC) (SEQ ID NO:9) from the MP-52 sequence. The amplification products were reamplified using the same adapter primer and an overlapping internal primer (TCCAGGGCACTAATGTCAAACACG) (SEQ ID NO:10) from the MP-52 sequence. Subsequently the reamplification products were reamplified using an overlapping adapter primer (ATTCGCATGCCATGGTCGACGAAG) (SEQ ID

NO:5) and an overlapping internal primer (ACTAATGTCAAACACGTACCTCTG) (SEQ ID NO:11) from the MP-52 sequence. The final reamplification products were cloned with blunt ends into a vector (Bluescript SK, Stratagene No. 212206) which had been cleaved with EcoRV. The clones were characterized by their sequence overlapping with the DNA of λ 2.7.4.

Please amend the paragraph spanning pages 21 and 22 of the specification as follows.

For this the HindIII fragment from plasmid pSK52s that starts with nucleotide 576 in SEQ ID NO. 1, was isolated and the protruding ends were made blunt by treatment with Klenow fragment. A Not I restriction cleavage site was introduced at both ends of the fragment by ligation of the adapter.

Adapter: AGCGGCCGCT (SEQ ID NO:12)

TCGCCGGCGA (SEQ ID NO:41)

Vector pABWN was restricted with XhoI, also treated with the Klenow fragment and dephosphorylated with intestinal alkaline phosphatase from the calf (Boehringer Mannheim). The same phosphorylated adapter was ligated on so that an insertion of the MP52 fragment after restriction with NotI into the generated Not I cleavage site of the vector was now possible. The expression vector that results is subsequently denoted HindIII-MP52/pABWN. All the reactions carried out for the cloning were carried out according to standard methods (e.g. CP units 3.16).